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Critical Windows of Maternal Exposure to Biothermal Stress and Birth Weight for Gestational Age in Western Australia

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Background: There is limited and inconsistent evidence on the risk of ambient temperature on small for gestational age (SGA) and there are no known related studies for large for gestational age (LGA). In addition, previous studies used temperature rather than a biothermal metric.

Objectives: Our aim was to examine the associations and critical susceptible windows of maternal exposure to a biothermal metric [Universal Thermal Climate Index (UTCI)] and the hazards of SGA and LGA.

Methods: We linked 385,337 singleton term births between 1 January 2000 and 31 December 2015 in Western Australia to daily spatiotemporal UTCI. Distributed lag nonlinear models with Cox regression and multiple models were used to investigate maternal exposure to UTCI from 12 weeks preconception to birth and the adjusted hazard ratios (HRs) of SGA and LGA.

Results: Relative to the median exposure, weekly and monthly specific exposures showed potential critical windows of susceptibility for SGA and LGA at extreme exposures, especially during late gestational periods. Monthly exposure showed strong positive associations from the 6th to the 10th gestational months with the highest hazard of 13% for SGA (HR = 1.13; 95% CI: 1.10, 1.14) and 7% for LGA (HR = 1.07; 95% CI: 1.03, 1.11) at the 10th month for the 1st UTCI centile. Entire pregnancy exposures showed the strongest hazards of 11% for SGA (HR = 1.11; 95% CI: 1.04, 1.18) and 3% for LGA (HR = 1.03; 95% CI: 0.95, 1.11) at the 99th UTCI centile. By trimesters, the highest hazards were found during the second and first trimesters for SGA and LGA, respectively, at the 99th UTCI centile. Based on estimated interaction effects, male births, mothers who were non-Caucasian, smokers, ≥35 years of age, and rural residents were most vulnerable.

Conclusions: Both weekly and monthly specific extreme biothermal stress exposures showed potential critical susceptible windows of SGA and LGA during late gestational periods with disproportionate sociodemographic vulnerabilities. https://doi.org/10.1289/EHP12660

Introduction

Small for gestational age (SGA) and large for gestational age (LGA) are defined as birth weight < 10th and > 90th centiles, respectively, with reference to population-based birth weight at the same gestational age and sex.[1] SGA and LGA are common risk factors of perinatal mortality and various morbidities from birth to adulthood. For example, the risk of neurodevelopmental delay, cardiometabolic disorders, and immunologic dysregulation are higher among births with SGA and LGA.[2–5] Common risk factors of SGA and LGA include fetal factors (e.g., genetic diseases, male fetus), uteroplacental factors (e.g., structural placental factors, reduced blood flow), and maternal factors or conditions (e.g., race/ethnicity, smoking, maternal age).[1] Moreover, exposure to ambient and indoor air pollution,[6,7] other chemicals,[8,9] and, recently, climatic factors are modifiable environmental risk factors of SGA and LGA of increasing interest.[10,11]

The increasing severity of the climate change crisis[12] is being recognized as a serious threat to reproductive health.[13,14] Pathophysiologically, thermal stress exposures increase dehydration and induce oxidative stress and systemic inflammatory responses, leading to adverse reproductive and fetal health outcomes.[15–17] Several recent observational studies reported on maternal exposure to ambient temperature and pregnancy outcomes, such as pregnancy complications, preterm birth, stillbirth, and low birth weight.[11,18] However, related research is limited and with inconsistent findings on SGA.[10,19–21] For LGA, to the best of our knowledge, related epidemiologic evidence is currently lacking in the literature, but this is now receiving greater attention in air pollution epidemiology.[22–24] It is important to investigate the association between climate change extremes and LGA risk for actionable intervention given that LGA is also implicated with many health outcomes throughout the life course.[1,25–27]

The timing of environmental exposure is clinically important to determine the specific nature of the dose–response relationship and critical environmental thresholds and windows.[17,28] Previous studies investigated average trimesters and entire pregnancy exposures[19–21] and could not detect fine temporal critical periods of susceptibility of the exposure.[28] In addition, regressing the outcome on each of the three trimester-average exposures increases the potential to yield biased estimates and identify incorrect critical windows.[28] Distributed lag linear or nonlinear models (DLNMs) were proposed to produce more accurate estimates and for flexible identification of fine temporally resolved critical windows.[28–30] Among the few studies on ambient temperature and the risk of SGA,[10,19–21] only one study used this high-quality method to assess weekly prenatal ambient temperature and heat index (ambient temperature and dew point) and the odds of SGA.[10]

Ambient temperature or apparent temperature are traditionally used to assess thermal stress exposure in epidemiological studies.[11,18] However, it is well known that the human body does not selectively perceive and respond to an individual climatic factor and that human thermophysiology is not a function of only air temperature.[31] Thus, rather than only considering singular air temperature, it has been suggested that estimation of thermal–

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health outcomes should be based on thermophysiological metrics (hereon, biothermal metrics) that account for the total thermal environment (air temperature, radiant temperature, humidity, and wind), activity (metabolic heat production), and clothing properties.[31–33] Several comparative studies[34–36] and a comprehensive evaluative study[32] have been conducted and four biothermal metrics were recommended recently as appropriate for thermal–health studies and warning systems.[32] Among them, the modern Universal Thermal Climate Index (UTCI) was reported most suitable because it best simulates the thermal response of the human body and has relatively high climatic sensitivity.[34,35,37,38] Recent applications of UTCI in thermal–health warning systems, operational weather forecasting, medical, and epidemiologic fields have been reviewed elsewhere.[39,40] So far, few studies have applied biothermal metrics in perinatal epidemiology,[41–45] and none for SGA and LGA.

To address the stated limitations, we assessed space–time-varying UTCI from preconception periods[46,47] to birth and applied Cox proportional hazard (Cox PH) regression nested within DLNM[24,29,30] to examine the maternal exposure to average weekly, monthly, and cumulative UTCI and the hazards of SGA and LGA. We identified potential critical periods of susceptibility and sociodemographically vulnerable subpopulations to inform targeted clinical and public health interventions.

Methods

Study Area, Design, and Population

Western Australia is the largest state by area in Australia, covering 2.6 million km^2 with a total population of 2.8 million.[48] We conducted a population-based retrospective cohort study from 1 January 2000 to 31 December 2015 in Western Australia using a de-identified Midwives Notification System (MNS) from the Western Australia Department of Health. The MNS is a statutory routine birth records data collection system that includes all births with ≥20 completed gestational wk or ≥400 g fetal weight if the gestational length is unknown.[49] The MNS contains sociodemographic and clinical information on both mother and baby, including maternal residential address as statistical area level 1 (SA1) at the time of birth delivery. The second smallest geographical unit in Australia, the SA1s are variable in geographic size with a median of 19 hectares and an average population of 400 individuals.[50] From a total of 474,835 births, we excluded births with missing SA1 ($n=35{,}352$), gestational age ($n=1{,}021$) or sex ($n=5$). We also excluded multiple births ($n=13{,}018$), births with questionable birth weight of <400 g or >6,000 g ($n=858$),[51,52] gestational age outside the range of 22–42 completed wk ($n=768$), and births to mothers >50 years of age ($n=7$). To account for the potential fixed or truncated cohort bias,[53,54] we created a cohort defined by the date of conception and further excluded pregnancies with conception dates <22 wk before the beginning of the cohort (women who conceived before 31 July 1999, $n=7{,}309$) and at >42 wk before the cohort ended (women who conceived after 12 March 2015, $n=1{,}433$).[54,55] Five births that did not have a compatible address for exposure assignment were excluded. The final sample included in this study was 385,337 singleton term births (Figure S1). Using term births enabled estimation of direct effects of the exposure on fetal growth independent of preterm birth,[19,56,57] as well as complete exposure histories up until the 37th completed gestational wk for all births to minimize bias.[58]

Outcomes Assessment

Adverse birth weight for gestational age outcomes considered were SGA and LGA. Gestational age was calculated from the perinatal records as the difference between the date of birth and start of pregnancy based on the best available clinical estimates from ultrasonography, or last menstrual period if ultrasound was not available. SGA and LGA were defined as births with birth weight below the 10th centile and above the 90th centile, respectively, for specific gestational age and sex using the study population.

Covariates

The covariates, including sociodemographic factors, biological factors, and medical or clinical information on both mothers and neonates were selected a priori from the birth records as potential confounders based on biological and epidemiological evidence in the literature[18,24,52,55,59] and availability in our data set. This included sex (male or female), year index variable for year of conception (1999 = 1 to 2015 = 17), calendar month of conception (1 to 12), maternal age as a continuous variable, marital status (married or unmarried), smoking during pregnancy (nonsmoker or smoker), parity (nulliparous or multiparous), and a remoteness indicator (urban or rural). Several race/ethnicity categories were originally defined in the birth record data. These were Caucasian, Asian, Indian, African/Negroid, Polynesian, Maori, Aboriginal/Torres Strait Islander, Aboriginal not Torres Strait Islander, Torres Strait Islander not Aboriginal, Aboriginal and Torres Strait Islander, and Other.[49] However, because of the small sample size for some minority groups and ethical concerns, race/ethnicity was categorized as Caucasian (European ancestry) or non-Caucasian. The area-level Index of Relative Socioeconomic Disadvantage derived by the Australian Bureau of Statistics[60] was assigned to the maternal residence at the time of delivery and categorized into tertiles to define high, moderate, and low socioeconomic status (SES). The few births without smoking status ($n=7$), SES ($n=21$), and the remoteness indicator ($n=134$) were assigned a separate category as "unknown."

Exposure Assessment

Biothermal stress was assessed using UTCI from the global gridded fifth generation of the European Centre for Medium-Range Weather Forecasts–Human analysis thErmAl comforT (ERA5-HEAT) reanalysis data set.[61] UTCI is an equivalent air temperature (in degrees Celsius) under reference conditions that has the same thermophysiological impact on humans under actual thermal environment.[37] UTCI was developed based on the advanced Fiala's multi-node human physiology and thermal comfort model that includes the complete human heat budget and thermophysiological response of an average person under reference conditions.[32,37,62] The reference nonmeteorological conditions are based on a person walking at a speed of 4 km/h and a rate of metabolic heat production of 2.3 metabolic equivalents of task (MET) (i.e., 135 W/m^2). The meteorological reference conditions are wind speed of 0.5 m/s measured at 10 m above the ground, mean radiant temperature equal to air temperature (no thermal irradiation), and a relative humidity of 50% or a constant vapor pressure of 12 hPa (relative humidity was capped at a vapor pressure of 20 hPa for air temperature >29°C).[38] As described in detail elsewhere,[61] UTCI at an hourly time step and $0.25^\circ \times 0.25^\circ$ (~ 25 km $\times$ 25 km) spatial resolution was calculated via a 6-order polynomial equation with four gridded input data: mean radiant temperature and ERA5 retrievals for both air temperature and relative humidity at 2 m above ground level, and for wind speed at 10 m above ground level with reference to thermophysiological and heat exchange conditions.[37,38,61] In this study, we obtained 24-h averages for daily gridded UTCI from the Copernicus Climate Data Store[61] between 1 January 1999 and 31 December

2015 over Australia and processed the UTCI at the SA1 levels in Western Australia using ArcGIS software (version 10.8.1; Esri).

For each birth, we assigned daily UTCI exposures from 12 wk preconception[21,24,47] through to birth based on dates of conception and birth and SA1 of the maternal residential address. Weekly (7-d average) exposures were calculated from 12 wk before conception (−11 to 0 wk) to birth (1 to 42 wk). For births with gestational age of <42 wk, exposure was set at zero for the weeks after delivery.[24,63,64] The maximum number of exposure weeks was therefore 54. Although collinearity is minimized in DLNM methodology, the results of the individual weeks in DLNM could still be biased by temporal collinearity,[65,66] and we also do not know which exposure period assessments (weeks, months, or trimester) is more relevant to identify the critical susceptible period for a given exposure–outcome relationship. We, therefore, additionally assessed monthly exposure from 3 months (90 d) preconception to birth by assuming that each gestational month has 30 d. Trimester-specific UTCI averages (1–13, 14–26, and 27–birth delivery gestational wk) and other cumulative exposures, such as preconception through pregnancy, entire pregnancy (conception to birth), and preconception (average of 12 wk before pregnancy), were also calculated.

Statistical Analyses

Main and subgroup analyses. We applied DLNMs with Cox PH regression to estimate weekly and monthly specific time-varying effects of maternal exposure to biothermal stress (using the UTCI) on SGA and LGA by using gestational age in weeks as the underlying timescale and each SGA and LGA as a dichotomous outcome.[24,63,67–71] The modeling framework is described according to the following formula:

$$h_i(t|x, C) = h_0(t)\exp(\beta x_t + \mathcal{B}C),$$

where h is the hazard; i is the ith birth; x denotes the cross-basis matrix for weekly or monthly biothermal stress exposure at week or month t and the lags; C denotes the set of covariates; β and $\mathcal{B}$ are coefficients of the exposure and covariates, respectively; and $h_0(t)$ denotes the baseline fetal growth hazard at week or month t (i.e., the hazard function for a birth whose exposures and covariates are all equal to 0). The bidimensional cross-basis function was constructed with the DLNM framework for simultaneous analysis of weekly or monthly exposure–lag–response associations[29,30] to identify potential critical susceptible exposure windows.[24,67,68] To flexibly capture any nonlinear and delayed effects of the biothermal stress, both exposure–response and lag–response associations (maximum lag was set at 54 wk) were modeled as natural cubic splines with several combinations of 2 to 7 degrees of freedom (df), assuming smooth variation across exposure periods. The linear relationship of the exposure–response function was also tested. Based on the minimum Akaike Information Criterion (AIC) comparisons, dfs of 6 and 3 for exposure–response and lag–response associations, respectively, were used for the final analyses.[29,30,72] We estimated both weekly and monthly hazard ratios (HRs) and the 95% confidence intervals (95% CIs).[24,67,68] We first employed the Schoenfeld residual test to check the assumptions of the Cox PH model and specified time-by-covariate interaction terms for covariates that violated the proportional hazards assumption.[67,73,74] The HRs (95% CIs) of the biothermal stress exposures at the moderate (10th, 90th centiles), severe (5th, 95th centiles), and extreme (1st, 99th centiles) of UTCI exposures, using median UTCI as the reference, were estimated.[71]

Furthermore, cumulative effects of the biothermal stress during preconception, entire pregnancy, and each trimester-average exposure were also evaluated using separate standard Cox PH models without the cross-basis function of the exposure. Average exposures for the preconception and entire pregnancy periods were included together to minimize the bias in the effect estimates if separate models were used. Similarly, all three trimester exposures were included simultaneously in the model instead of separate models for each trimester-average exposure.[28,54,59] To estimate the nonlinear effect of each cumulative exposure period with a standard Cox PH model, we used the *one-basis* function of the *dlnm* R package to construct unidimensional or nonlagged exposure–outcome associations using natural splines with the following dfs based on lowest AIC[29,30,72]: 5 df for preconception and entire pregnancy and 2 df for the three trimester-average exposures for SGA, and 2 df for all cumulative exposures for LGA. All the models were adjusted for the potential confounders described earlier. Maternal age was modeled as a continuous variable using natural splines with 3 df.[75,76]

To explore the potential for effect modification, we conducted stratified analyses by infant sex (male or female), race/ethnicity (Caucasian or non-Caucasian), maternal age at delivery (<35 or ≥35 years of age), SES (high, moderate, low), remoteness (urban or rural), maternal smoking status (nonsmoker or smoker), parity (nulliparous or multiparous), and pregnancy complications (yes or no for gestational diabetes, preeclampsia, placental abruption, premature rupture of membrane, asthma, urinary tract infection, threatened miscarriage, and threatened preterm birth). These analyses used preconception-through-pregnancy cumulative exposure. The HRs (95% CIs) at the 1st and 99th centiles, relative to the median UTCI were estimated for each subgroup and further compared as the ratio of hazard ratios (RHRs, with 95% CIs) by performing the Altman and Bland test of interaction.[77,78]

Sensitivity Analyses

Several sensitivity analyses were performed to ascertain the credibility of the weekly specific results. *a*) Mean rather than median UTCI was used as the reference. *b*) The dfs in the natural cubic spline was increased by one (that is 7 for exposure predictor and 4 for lag period) in the cross-basis function of the DLNM. *c*) Maternal age was included as a categorical variable (≤19, 20–34, ≥35 years of age) instead of as a natural spline of the continuous covariate. *d*) Seasonality was adjusted with four-season categories (fall, winter, spring, summer) instead of calendar month index. *e*) Weekly exposures from conception to birth were analyzed (that is, preconception exposures were excluded). *f*) Trimester-average exposures were analyzed in three separate models instead of concurrent analysis in a single model. *g*) All eligible singleton births with 22–42 gestational wk were analyzed. *h*) Logistic regression was used instead of Cox regression as reported in the only available previous study that implemented DLNM methodology for temperature and SGA.[10]

All statistical analyses were performed using the statistical software R (version 4.2.1; R Development Core Team), and main R packages *dlnm* and *survival* were used. We reported and interpreted the HRs (95% CIs) without considering any statistically significant threshold, as recommended by the American Statistical Association.[79] The R codes are provided in the Supplemental Material ("Appendix 1. R syntax for DLNMs Cox regression").

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval has been obtained from the Human

Table 1. Maternal characteristics of included singleton term births in Western Australia, 2000–2015 ($N = 385,337$).

Characteristics	*n* (%)
SGA	
No	347,632 (90.2)
Yes	37,705 (9.8)
LGA	
No	347,114 (90.1)
Yes	38,223 (9.9)
Infant sex	
Male	196,384 (51.0)
Female	188,953 (49.0)
Maternal age (y)	
≤19	17,170 (4.5)
20–34	291,366 (75.6)
≥35	76,801 (19.9)
Race/ethnicity	
Caucasian	303,375 (78.7)
Non-Caucasian[a]	81,962 (21.3)
Marital status	
Married	337,801 (87.7)
Unmarried	47,536 (12.3)
Pregnancy complications	
No	244,238 (63.4)
Yes	141,092 (36.6)
Smoker	
No	330,651 (85.8)
Yes	54,679 (14.2)
Unknown	7 (0.0)
Parity	
Nulliparity	160,731 (41.7)
Multiparity	224,606 (58.3)
Remoteness indicator	
Urban	238,826 (62.0)
Rural	146,377 (38.0)
Unknown	134 (0.0)
SES	
High	127,831 (33.2)
Moderate	128,439 (33.3)
Low	129,046 (33.5)
Unknown	21 (0.0)
Season of conception	
Fall	93,678 (24.3)
Winter	97,982 (25.4)
Spring	97,250 (25.2)
Summer	96,427 (25.0)

Note: LGA, large for gestational age at >90% birth weight; SES, socioeconomic status; SGA, small for gestational age at <10% birth weight.
[a]Non-Caucasian included races or ethnicities defined in the birth record as Asian/Indian ($N = 36,303$), African/Negroid ($N = 5,149$), Aboriginal/Torres Strait Islander/Polynesian/Maori ($N = 24,161$), and Other ($N = 16,349$).

Research Ethics Committees (HREC) at Curtin University (#HRE2020-0523) and Western Australia Department of Health (#2016/51). Participants' informed consent was waived given that we used retrospective routinely collected de-identified data sets, obtaining retrospective consent was impractical for our large cohort, and it was deemed by the HRECs that the benefits of this study outweighed the risk of harm.

Results

Characteristics of Study Population and Biothermal Stress Exposure

This study included 385,337 singleton term births, of which 37,705 (9.8%) were SGA and 38,223 (9.9%) were LGA. Slightly more than half of the births were male (51.0%), and the majority were born to mothers who were Caucasian (78.7%), married (87.7%), nonsmokers (85.8%), multiparous (58.3%), and urban residents (62.0%) and had a complicated pregnancy (63.4%). Mothers were almost equally distributed among the four seasons of conception (Table 1). The average exposure to UTCI (biothermal stress) over the full exposure period ranged from 8.1°C to 30.0°C with approximately equal mean (14.5 ± 2.5°C) and median (14.2°C). The UTCI distributions for the exposure periods tended to be within the range of 9–26°C, consistent with the standard categories of no thermal stress.[80] The specific average exposures for preconception, pregnancy, and each trimester were similar to the overall preconception to birth exposures over the 12-wk preconception through pregnancy periods. The number of births exposed at the 1st, 5th, 10th, 90th, 95th, and 99th centiles of UTCI were 663, 1,379, 3,485, 5,657, 175, and 290 births, respectively (Table 2).

Biothermal Stress Exposures and the Hazards of Term SGA and LGA

Compared with the median UTCI (14.2°C) as reference, exposure to various centile thresholds of weekly UTCI showed lower hazards of SGA during preconception periods up to the 10th gestational week and then increased thereafter up to birth, especially for 1st (10.3°C) and 95th (17.3°C) centiles exposure. Strong positive associations were found toward the end of pregnancy. For example, a 2% higher hazard of SGA was found at the 42nd gestational wk (HR = 1.02; 95% CI: 1.01, 1.04) for the 1st centile exposure (Figure 1; Table S1). As compared with the median exposure, weekly UTCI exposure showed very small positive associations or almost no association with the hazard of LGA (Figure 1). The strongest positive association was a 1% higher hazard of LGA (HR = 1.01; 95% CI: 1.00, 1.02) during the 36th–42nd gestational wk period for exposure to the 95th centile relative to the median UTCI (Table S2). Monthly UTCI exposure showed similar patterns but with stronger magnitudes of positive associations than the weekly exposure. The critical susceptible periods were 6th–10th gestational months, especially for 1st centile exposure, as compared with the median exposure with the strongest HRs of 13% for SGA (HR = 1.13; 95% CI: 1.10, 1.14) and 7% for LGA (HR = 1.07; 95% CI: 1.03, 1.11) in the 10th month (Figure 2; Tables S3 and S4).

As compared with the median UTCI, cumulative exposures (preconception through to birth, preconception, and entire pregnancy) generally showed negative associations at the 1st centile exposure but positive associations at the 99th centile exposure.

Table 2. Descriptive statistics of the average UTCI (in degrees Celsius) during each exposure period, from 12 wk preconception through delivery, for included singleton term births in Western Australia, 2000–2015 ($N = 385,337$).

Exposure periods	Min	Mean ± SD	Median	P1	P5	P10	IQR	P90	P95	P99	Max
Preconception through pregnancy[a]	8.1	14.5 ± 2.5	14.2	10.3	11.9	12.8	1.2	15.4	17.3	26.0	30.0
Preconception only	1.4	14.4 ± 5.2	14.0	5.8	7.6	8.2	8.8	20.8	22.0	29.4	35.8
Entire Pregnancy	6.6	14.5 ± 2.8	14.2	9.7	11.3	11.9	2.9	16.7	18.0	26.7	32.7
Trimester											
First	1.7	14.5 ± 5.2	14.2	5.9	7.7	8.3	8.9	20.9	22.0	29.6	36.0
Second	1.6	14.6 ± 5.1	14.2	6.1	7.8	8.5	8.7	20.9	22.0	29.8	36.1
Third	1.7	14.5 ± 5.1	14.1	6.1	7.7	8.4	8.7	20.8	21.9	29.6	35.6

Note: max, maximum; min, minimum; IQR, interquartile range = P75–P25; P1–P99, 1st–99th centiles; SD, standard deviation; UTCI, Universal Thermal Climate Index.
[a]Number of births at the 1st to 99th centiles of UTCI exposure were 663, 1,379, 3,485, 5,657, 175, and 290 births, respectively.

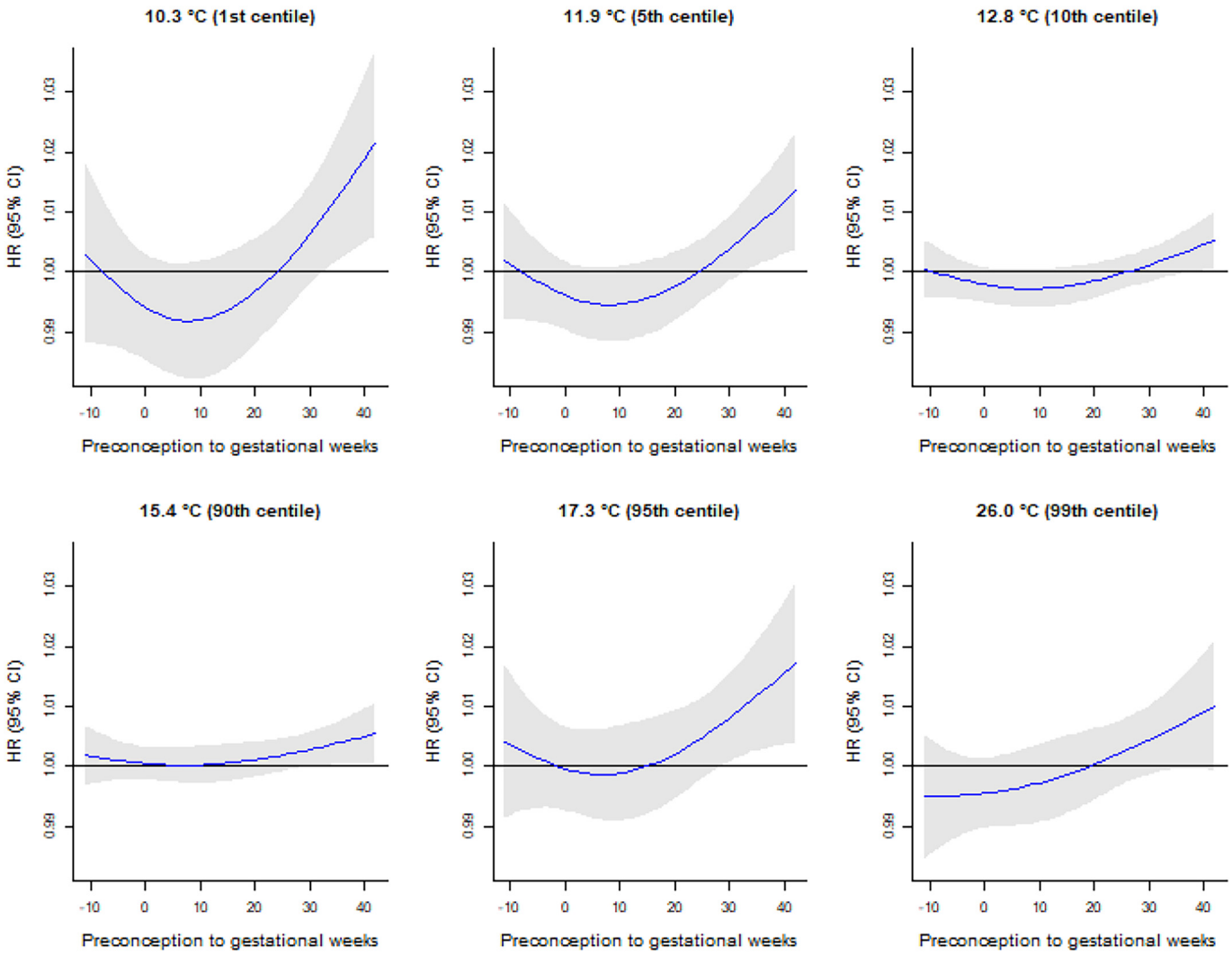

Figure 1. Adjusted HRs of SGA and LGA associated with the weekly specific UTCI over the 12-wk preconception (−11 to 0) through to gestational week at delivery (1 to 42) at different thresholds of UTCI using the median of 14.2°C as reference. Solid blue lines represent point estimates, and the shaded area represents 95% CIs. DLNM Cox proportional hazard models were adjusted for infant sex, maternal age, race/ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception. Numeric data can be found in Tables S1 and S2. Note: CI, confidence interval; DLNM, distributed lag nonlinear models; HR, hazard ratio; LGA, large for gestational age at >90% birth weight; SGA, small for gestational age at <10% birth weight; UTCI, Universal Thermal Climate Index in degrees Celsius.

The strongest hazards were 11% higher hazard of SGA during the entire pregnancy (HR = 1.11; 95% CI: 1.04, 1.18) and 4% higher hazard of LGA during preconception through to birth (HR = 1.04; 95% CI: 0.98, 1.11) at 99th centile as compared with the median exposure. Preconception exposure showed small magnitude of higher hazard, particularly at the 1st centile exposure for SGA and the 99th centile exposure for LGA (Table 3; Table S5 and Figure S2). For trimester-average exposures, the strongest hazards were 8% higher hazard of SGA during the second trimester (HR = 1.08; 95% CI: 1.00, 1.17) and 10% higher hazard of LGA during the 1st trimester (HR = 1.10; 95% CI: 1.03, 1.18) for exposure to 99th centile as compared with the median exposure (Table 3; Table S5 and Figure S3).

We observed higher hazards of adverse fetal growth in some vulnerable subpopulations for exposures at the 1st and 99th centiles as compared with the median UTCI, particularly for SGA at the 99th centile exposure (Table S6). Comparing the RHRs between groups showed elevated hazard at the 99th centile exposure for SGA (RHR = 1.07; 95% CI: 0.96, 1.19) and at the 1st centile exposure for LGA (RHR = 1.02; 95% CI: 0.93, 1.13) in male births. The hazard was elevated in non-Caucasians for SGA (RHR = 1.28; 95% CI: 1.16, 1.40) at the 99th centile exposure, but there was no obvious difference for LGA. The hazard was elevated for SGA (RHR = 1.10; 95% CI: 0.96, 1.25) and slightly lowered for LGA (RHR = 0.87; 95% CI: 0.73, 1.05) in unmarried mothers at the 99th centile exposure. For mothers ≥35 years of age, the hazard was elevated slightly at the 1st centile exposure for SGA (RHR = 1.01; 95% CI: 0.84, 1.21) and elevated for LGA at both the 1st centile exposure (RHR = 1.09; 95% CI: 0.96, 1.23) and the 99th centile exposure (RHR = 1.04; 95% CI: 0.88, 1.23). The hazard was elevated for SGA at the 1st centile exposure in mothers with moderate SES (RHR = 1.02; 95% CI: 0.81, 1.29) and for LGA at 99th centile exposure in mothers with low SES (RHR = 1.15; 95% CI: 0.99, 1.34) as compared

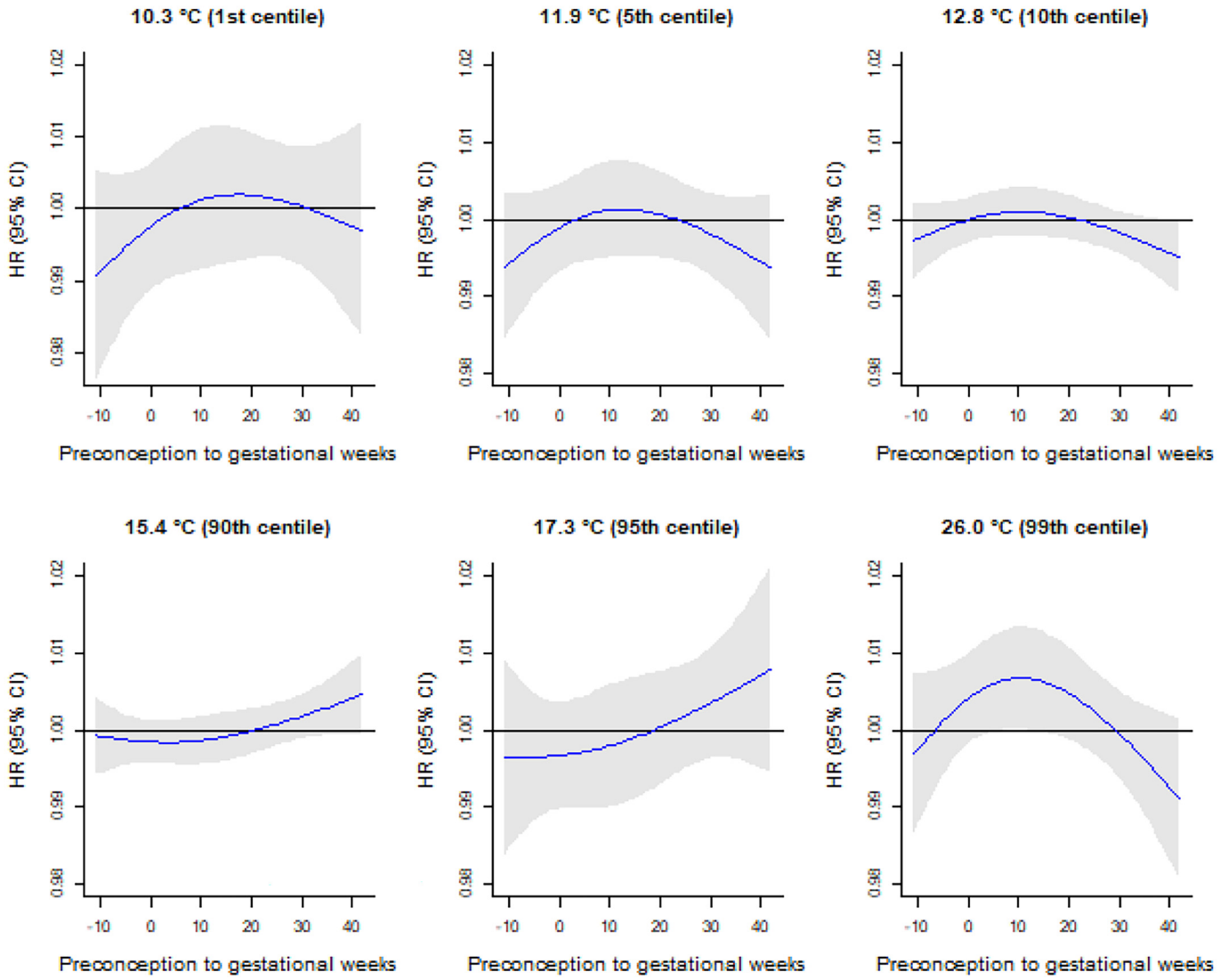

Figure 1. (*Continued.*)

with high SES residents. The hazard was elevated, although with extremely high imprecision, at the 99th centile exposure for SGA (RHR = 36.67; 95% CI: 1.52, 888.54) and at the 1st centile exposure for LGA (RHR = 1.45; 95% CI: 1.04, 2.04) in rural residents. The hazard was greater for SGA (RHR = 1.22; 95% CI: 1.09, 1.37) and LGA (RHR = 1.03; 95% CI: 0.87, 1.06) at the 99th centile exposure in mothers who smoked during pregnancy. The hazard was elevated for SGA at the 1st centile exposure (RHR = 1.12; 95% CI: 0.99, 1.27) but lowered slightly for LGA at both the 1st and the 99th centiles exposure in nulliparous mothers. There was no obvious difference for SGA, but the hazard was elevated in mothers with pregnancy complications for LGA at the 99th centile exposure (RHR = 1.21; 95% CI: 1.06, 1.38) (Table 4).

Sensitivity Analyses

Our results did not change substantially after altering modeling conditions (Figures S4–S9, Excel Tables S1–S12). In addition, results of the trimester-average exposures analyzed in three separate models showed higher hazards of SGA and LGA in second and first trimesters, respectively (Figure S10 and Excel Table S13) as found in the main analysis for the concurrent analysis of all trimester-average exposures in a single model. Finally, the results from DLNM logistic regressions were consistent with that of the DLNM Cox PH regression (Figures S11 and Excel Tables S14 and S15).

Discussion

Associations between Biothermal Stress and the Hazards of Term SGA and LGA

This is the first study, to the best of our knowledge, to use a biothermal stress metric (i.e., UTCI) to evaluate weekly and monthly specific preconception to birth exposures and the hazards of term SGA and LGA. Both weekly and monthly specific exposures showed similar patterns of the association with higher hazards of adverse fetal growth, especially for SGA, which increased toward the end of the pregnancy. Monthly specific exposures showed higher HRs than weekly specific exposures at 6–10 gestational months, especially at the 1st centile exposure compared

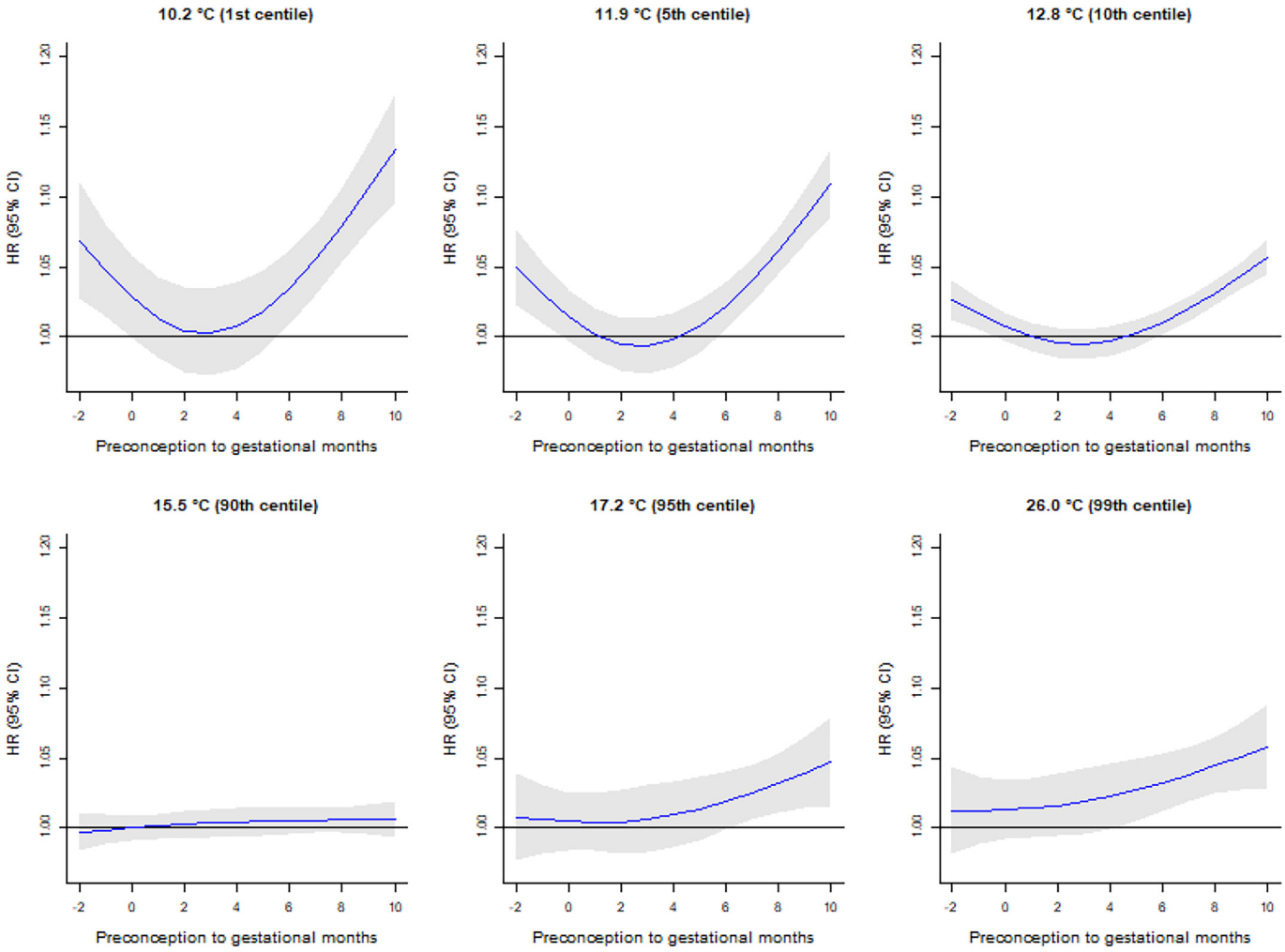

Figure 2. The exposure–response association between maternal monthly specific UTCI exposures for 3 months preconception through to gestational month at delivery with reference to median 14.2°C and the HR (95% CI) of SGA and LGA. Numeric data can be found in Tables S3 and S4. DLNM Cox proportional hazard models were adjusted for infant sex, maternal age, race/ethnicity, marital status, parity, maternal smoking, remoteness, areal-level socioeconomic status, year, and month of conception. Note: CI, confidence interval; DLNM, distributed lag nonlinear models; HR, hazard ratio; LGA, large for gestational age at >90% birth weight; SGA, small for gestational age at <10% birth weight; UTCI, Universal Thermal Climate Index in degrees Celsius.

with median exposure, suggesting potential critical windows of susceptibility for both SGA and LGA. The cumulative preconceptional exposure analysis showed positive associations, particularly for LGA at higher exposure. Entire pregnancy and trimester-average exposures showed relatively strong positive associations at the 99th centile exposure as compared with the median exposure for both SGA and LGA. The trimester-average exposures showed the strongest HRs during the second and first trimesters for SGA and LGA, respectively. The identified higher-risk subpopulations were male births, and births by mothers who were non-Caucasian, smokers, and rural area residents for both SGA and LGA. Births by mothers ≥35 years of age were at higher hazards, especially for LGA at both extreme thresholds of exposure. Births by mothers with moderate SES were at higher hazard of SGA, whereas mothers with low SES were at a higher hazard of LGA as compared with those with a high SES.

Results from few previous studies, with inconsistent findings are available for comparison for SGA[10,19–21] but none for LGA, to the best of our knowledge. Of these, only one study reported weekly heat metrics (mean temperature and mean heat index) and the odds of SGA on 4,442 births in Boston, USA.[10] Contrary to our findings, that study found essentially no obvious association of either mean temperature or mean heat index with the odds of SGA for a 5°C increase in mean weekly specific exposures. The authors, however, found positive associations for weekly specific and cumulative exposures with a 1°C increase in standard deviation of temperature and heat index where the strongest odds of SGA were found between the 9th–26th gestational wk and the second trimester.[10] This could imply that the low variability in the mean weekly temperature or simple heat index exposure was insufficient to detect any clear association with SGA. This could also explain why we found stronger positive associations with monthly than weekly specific exposures. Because changes in birth weight for gestational age may not be obvious within short intervals, monthly specific exposure assessment could better detect susceptible critical periods of the impact of thermal stress on SGA and LGA. However, weekly specific higher temperatures have been associated with impaired ultrasound anthropometric measurements, such as biparietal diameter, head circumference, femur length, abdominal circumference, and term birth weight.[58] Importantly, temperature or simple

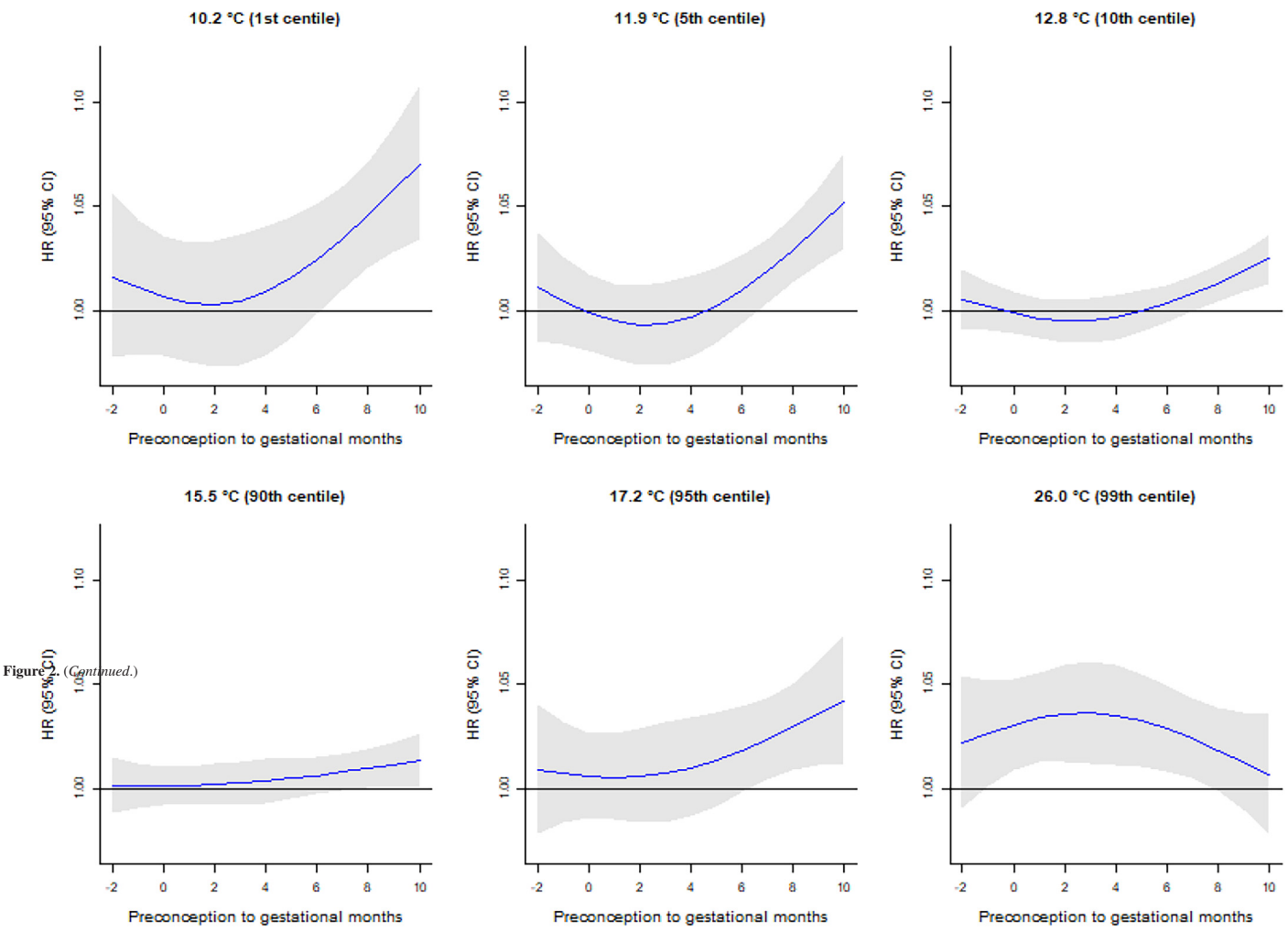

Figure 2. (*Continued.*)

heat index could have underestimated the effects of the exposure as compared with using UTCI.[32,33] These differences have been reported in other thermal–health outcomes studies that compared the UTCI with other thermal metrics (including temperature) with the recommendation to use UTCI in future studies,[81–83] supporting the recommendation in the recent reviews.[32,33,39]

Our results of lower hazards of SGA at low exposure thresholds and higher hazard at high exposure thresholds over the entire pregnancy period with similar magnitude was consistent with the results from a large cohort study conducted in the United States on nearly 30 million singleton term births.[19] That study found that entire pregnancy-average temperatures between the county-specific 80th–90th centile and above the 90th centile were associated with a 3% higher [odds ratio (OR) = 1.03; 95% CI: 1.02,1.04] and 4% higher (OR = 1.04; 95% CI: 1.03,1.054) odds of SGA, respectively, relative to 40th–50th centile exposure.[19] In contrast, an analysis of 56,141 singleton term births, including 15.4% term SGA in southern Israel reported that the highest quartile ambient temperature was associated with 9% lower odds of SGA (OR = 0.91; 95% CI: 0.84, 0.99), whereas the lowest quartile ambient temperature was associated with 18% higher odds of SGA (OR = 1.18; 95% CI: 1.09, 1.29) as compared with the two intermediate quartiles over the entire pregnancy.[20] Our findings showed that although preconceptional exposure showed no clear association with SGA as reported previously,[21] it showed small positive associations with LGA at high exposure levels.

Regarding the trimester-average exposures, our results were similar to that of a large cohort study that found that high temperature was associated with higher odds of SGA during both second and third trimesters (stronger in the second semester) and low temperature showed no association with relative odds of SGA.[19] Again, there were other discrepant findings, such as no associations with cumulative exposures by trimesters,[10,21] and high temperature associated with lower odds of SGA during first trimester and higher odds during third trimester.[20] Such discrepancies may be due to geographical differences in thermal or temperature distributions even within the same setting, acclimatization, adaptation or mitigation strategies, differences in study design, characteristics of study population, exposure assessment method, and exposure thresholds.[10,19,21,42] Trimester-specific results from all the previous studies were based on separate models for each trimester.[10,19–21] Our sensitivity results for the separate trimester-specific models were consistent with that of the main results that included all trimesters concurrently in a single model. Our findings from both weekly and monthly specific exposures indicated that late gestation periods are potential critical susceptible periods, which differed from our findings from trimester-average exposures

Table 3. The exposure–response association as HR (95 % CI) of SGA and LGA, between maternal cumulative UTCI exposures from preconception through pregnancy and over trimester-specific periods with reference to the median, 14.2°C.

Exposure period	UTCI centile	SGA	LGA
Preconception through pregnancy	P1	0.96 (0.90, 1.01)	0.94 (0.89, 0.98)
	P99	1.07 (1.01, 1.12)	1.04 (0.98, 1.11)
Preconception	P1	1.01 (0.96, 1.06)	0.94 (0.91, 0.98)
	P99	0.98 (0.91, 1.05)	1.03 (0.95, 1.11)
Pregnancy	P1	0.96 (0.91, 1.02)	0.97 (0.92, 1.01)
	P99	1.11 (1.04, 1.18)	1.03 (0.95, 1.11)
Trimester			
First	P1	1.00 (0.95, 1.05)	0.94 (0.89, 1.00)
	P99	1.00 (0.94, 1.06)	1.10 (1.03, 1.18)
Second	P1	0.98 (0.94, 1.02)	1.02 (0.98, 1.07)
	P99	1.08 (1.00, 1.17)	0.99 (0.91, 1.08)
Third	P1	0.99 (0.94, 1.05)	0.98 (0.92, 1.04)
	P99	1.03 (0.97, 1.10)	1.01 (0.94, 1.09)

Note: HR (95% CI) of SGA and LGA are reported at various percentiles of the exposure in Western Australia, 2000–2015. Standard Cox proportional hazards model was adjusted for infant sex, maternal age, race/ethnicity, marital status, parity, maternal smoking, remoteness, areal-level socioeconomic status, year, and month of conception. Preconception period was 12 wk prior to conception. CI, confidence interval; HR, hazard ratio; LGA, large for gestational age at >90% birth weight; P1–P99, 1st–99th centiles; SGA, small for gestational age at <10% birth weight; UTCI, Universal Thermal Climate Index in degrees Celsius.

Table 4. The estimated interaction effects as RHR (95% CI) of SGA and LGA, relative to the indicated reference subgroup over preconception through to pregnancy with cumulative exposure to 1st and 99th centiles of UTCI relative to median UTCI in Western Australia, 2000–2015.

Subgroup [*n* (%)]	UTCI centile	SGA	LGA
Male: 196,384 (51.0)	P1	0.96 (0.85, 1.08)	1.02 (0.93, 1.13)
[Ref: female: 188,953 (49.0)]	P99	1.07 (0.96, 1.19)	1.00 (0.88, 1.14)
Non-Caucasian: 303,375 (78.7)	P1	1.09 (0.94, 1.26)	0.87 (0.75, 1.00)
	P99	1.28 (1.16, 1.40)	1.00 (0.87, 1.15)
[Ref: Caucasian: 303,375 (78.7)]			
Unmarried: 47,536 (12.3)	P1	1.06 (0.90, 1.25)	0.94 (0.80, 1.10)
[Ref: married: 337,801 (87.7)]	P99	1.10 (0.96, 1.25)	0.87 (0.73, 1.05)
≥35 years of age: 76,801 (19.9)	P1	1.01 (0.84, 1.21)	1.09 (0.96, 1.23)
	P99	0.93 (0.79, 1.11)	1.04 (0.88, 1.23)
[Ref: <35 years of age: 308,536 (80.1)]			
Low SES: 129,046 (33.5)	P1	0.94 (0.66, 1.34)	1.03 (0.88, 1.21)
[Ref: high: 127,831 (33.2)]	P99	0.64 (0.55, 0.76)	1.15 (0.99, 1.34)
Moderate SES: 128,439 (33.3)	P1	1.02 (0.81, 1.29)	0.93 (0.80, 1.07)
	P99	0.78 (0.35, 1.73)	0.59 (0.31, 1.12)
[Ref: high: 127,831 (33.2)]			
Rural: 146,377 (38.0)	P1	2.11 (0.97, 4.57)	1.45 (1.04, 2.04)
[Ref: urban: 238,826 (62.0)]	P99	36.67 (1.52, 883.54)	2.20 (0.96, 5.04)
Smoker: 54,679 (14.2)	P1	0.99 (0.87, 1.13)	1.00 (0.86, 1.17)
[Ref: nonsmoker: 330,651 (85.8)]	P99	1.22 (1.09, 1.37)	1.03 (0.87, 1.22)
Nulliparity: 160,731 (41.7)	P1	1.12 (0.99, 1.27)	0.95 (0.85, 1.06)
[Ref: multiparity: 224,606 (58.3)]	P99	1.02 (0.90, 1.13)	0.89 (0.77, 1.03)
Complicated pregnancy: 141,092 (36.6)	P1	0.94 (0.83,1.06)	1.00 (0.90, 1.11)
	P99	1.00 (0.90, 1.11)	1.21 (1.06, 1.38)
[Ref: uncomplicated pregnancy: 244,238 (63.4)]			

Note: DLNM Cox proportional hazards model was adjusted for infant sex, maternal age, race/ethnicity, marital status, parity, maternal smoking, remoteness, areal-level SES, year, and month of conception. These analyses used preconception through pregnancy cumulative exposure. For each model, the subgroup of the covariate investigated was not adjusted for. CI, confidence interval; DLNM, distributed lag nonlinear models; LGA, large for gestational age at >90% birth weight; P1 and P99, 1st and 99th centiles; Ref, reference; RHR, ratio of hazard ratios; SES, socioeconomic status; SGA, small for gestational age at <10% birth weight; UTCI, Universal Thermal Climate Index.

where second and first trimesters were critical susceptible periods for SGA and LGA, respectively. This difference has been demonstrated in a simulation study and indicated that the analyses of trimester-average exposures could result in biased estimates and incorrect critical susceptible periods for which reason distributed lag model should be preferred to trimester-average exposure models.[28] For LGA, our findings are novel because there is currently no known such evidence in the literature, suggesting the need for further related studies on LGA to contribute to the evidence-base, which has also been proposed for studies on air pollution exposure.[22–24]

The differences in the sensitivity to exposures, degree of the climate extremes, population characteristics, such as sociodemographic and underlying health conditions, acclimatization, and adaptation or mitigation measures, determine the vulnerability of the population to biothermal stress exposures.[20,45] These could explain the high risks of adverse fetal growth in vulnerable subpopulations, such as male births and births by mothers who were non-Caucasian, smokers, of low or moderate SES, ≥35 years of age, and rural area residents. Male fetuses have low plasma anti-inflammatory capacity to counteract the inflammatory responses due to thermally induced oxidative stress.[84] Female fetuses also respond to reduced maternal nutrition and moderation in placental physiology and show a better response to higher levels of reactive oxygen species and maternal glucocorticoids than males, which may reduce the risk of adverse fetal growth in female births as compared with male births.[85] Higher risks in non-Caucasians, mothers with moderate or low SES, and rural area residents may be explained by factors such as underutilization of antenatal care services, lack of mitigation strategies (e.g., use of heating or cooling systems), and higher involvement in outdoor activities or outdoor work.[86] Racial/ethnic reproductive health inequalities have also been attributed to systemic discrimination, as well as residential and housing segregation.[87]

Appropriate public health interventions, such as actively raising the awareness of the risk of exposure to extreme climate events to minimize outdoor activities, use of air conditioning, the shift to sustainable non–fossil-based energy and greening the environment, thermal–health warning systems, and other climate governance policies, are required.[42,43,86,88] These measures are critically important for achieving the United Nations' Sustainable Development Goals 3 and 13[89] to ensure that the health outcomes at birth are not affected by the changing climate with serious health implications.[13,88,90]

Biological Mechanisms

The biological mechanisms of maternal exposure to thermal or biothermal stress and fetal growth have not been completely elucidated. However, *in vivo* studies provide convincing plausible pathophysiological pathways, particularly for fetal growth restriction resulting in SGA.[16,91,92] The general physiological changes during pregnancy and fetal metabolic activities increase thermal vulnerability of pregnant women that affect their thermoregulatory capacity.[43,93] Exposure to extreme thermal environments increases thermal strain during pregnancy, causing hypo- or hyperthermia. This can induce oxidative stress, heat shock, and inflammatory responses, and reduce uterine blood flow that affect placental growth, and cause placental dysfunction as demonstrated in experimental animal studies.[16,91,92] Consequently, both passive and active maternal-to-fetal transport of oxygen and nutrients is affected and has been observed to be profound at mid- to late-pregnancy periods.[15] These cause fetal hypoxemia and hypoglycemia, which slow fetal growth and alter fetal metabolic and endocrine activities, resulting in abnormal fetal growth.[15,17,91] It was also found that maternal inflammation at the mid-gestational

stage impairs myoblast (stem cell) function, increases protein catabolism, and reduces skeletal muscle growth near term.[92] Moreover, fetal growth restriction in ewes was found to be an adaptative mechanism at the expense of normal fetal growth and development to hyperthermia-induced placental insufficiency to preserve placental transport capacity of oxygen and nutrients.[91]

As compared with SGA, biological mechanisms linking environmental exposures, such as thermal stress to LGA is not well-understood, suggesting the need for more studies. The plausible causal pathways are the known processes by which oxidative stress and inflammation cause high blood glucose or hyperglycemia, which can be transported to the developing fetus. The fetus produces extra insulin, which together with the extra glucose or fetal hyperglycemia, can lead to increase fetal growth and fat deposition, resulting in an increased risk of LGA.[94,95]

Strengths and Limitations

Our study has several strengths. The use of the reportedly most suitable available biothermal metric (i.e., UTCI) and the exposure assessment with a spatially and temporally resolved grid are major strengths of this study. The space–time-varying exposure assessment reduces exposure misclassification as compared with the conventional use of simple models or proximity to sparse monitoring stations[18] that tend to be distant from where people reside, as well as excluding rural residents because monitoring stations are often sited in cities and urban areas.[20,42] Application of DLNM nested in Cox PH regression is a further strength because it allowed us to investigate the hazards of fetal growth at finer temporal scales (i.e., gestational weeks and months) that are less biased and may be biologically more relevant as compared with trimester-based periods of exposure to detect critical susceptible windows.[28,30] Given the limited related research on SGA,[11] no known previous evidence on LGA, and that no previous study used a biothermal stress exposure metric, our findings have added to and provided new epidemiological evidence to the literature.

Several limitations were also present in this study. Despite the strength of being able to assess the individual-level exposure at the second smallest geographical unit (i.e., the SA1), very fine spatial resolution can potentially also introduce misclassification owing to the lack of information on exposures in nearby areas, such as parks, shopping centers, and other local-level community centers that people access daily. So, it is potentially less accurate to assess exposure at very fine spatial resolution targeted to the exact place of residence. Residential mobility during pregnancy and activity–time patterns were not accounted for. A recent review on maternal relocation[96] and simulation study[97] found no impact of residential mobility on the effect estimates of the exposure on adverse birth outcomes. But a gold standard approach remains personalized real-time exposure assessment by using mobile thermal sensors.[98] However, this method is not feasible in large-scale studies. Possible nondifferential exposure misclassification due to residential mobility, inability to incorporate daily activity patterns, time spent outdoors or indoors, and use of air conditioning could have biased the observed results toward the null.[10,19,21] We did not have data on many other important confounding or covariate factors, such as maternal alcohol or illicit drug intake, educational level, nutritional status, employment, infection (e.g., seasonal influenza), maternal weight, height, and physical activity during pregnancy. A few of these factors, however, were partly controlled through the SES and remoteness variables. Both live and stillborn births were examined, but we did not have information on early pregnancy loss (miscarriages or spontaneous abortions), which could lead to underestimating the effect estimates. This is because biothermal stress in early gestational periods could preferentially result in early pregnancy loss for the fetuses that are more susceptible to the effects of the exposure on fetal growth.[54] In addition, given that the birth outcomes were assessed at birth, we were unable to examine the effect of the exposure on *in utero* fetal growth trajectory given that births with abnormal growth in early pregnancy could later catch up and appear normal at birth. Thus, routine ultrasound anthropometric measurements could provide some useful insight in future studies.[58] Because of the complex uncertainties in future climate change scenarios, geographical variability, acclimatization, adaptation, or mitigation strategies and changes in vulnerability of the underlying population, the present exposure–response associations could not be forecast into the future or extrapolated to other locations.[42,99]

Conclusion

Compared with the median UTCI exposure, both weekly and monthly specific exposures at extreme centiles showed potential critical windows of susceptibility of SGA and LGA that increased toward the end of pregnancy. Cumulative preconceptional exposure showed no association with the hazard of SGA, but an association was found with a higher hazard of LGA at high exposure levels. Entire pregnancy and trimester-specific average exposures showed relatively strong positive associations at higher exposure levels as compared with the median exposure for both SGA and LGA. The strongest elevation in hazards were found during the second trimester for SGA and during the first trimester for LGA. Male births, and births by mothers who were non-Caucasian, smokers, ≥35 years of age, and resided in moderate or low SES and rural areas were particularly vulnerable subpopulations who may require targeted thermal mitigation strategies and resource allocations. Further studies should take advantage of the leveraged technological advancements for application of biothermal metrics, such as UTCI, rather than the singular use of ambient temperature.[31–33,40]

Acknowledgments

S.D.N. conceived and designed the study with contributions from G.A.T., B.M., and G.P. G.P. obtained access to the birth data and provided important inputs during the formal data analysis. S.D.N. accessed and assessed the exposure data, conducted data curation and formal data analyses, and drafted the initial version of the manuscript. K.C. and M.Y.-S. contributed to exposure assessment. All authors contributed to critical review and editing and have approved the final version of the manuscript.

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The Universal Thermal Climate Index data is freely accessible from the Copernicus Climate Data Store (https://doi.org/10.24381/cds.553b7518). The birth data cannot be made publicly available due to the data access agreement, but it can be requested directly from the Department of Health, Western Australia (https://ww2.health.wa.gov.au/Articles/J_M/Midwives-Notification-System).

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